H:SEEFF (discussion)

DR. SELIGMAN: We have time for questions, comments for Dr. Seeff. Naga.

DR. CHALASANI: Leonard, do you think there's a role for challenge with a lower dose, especially for your deliberate and your continued challenge, perhaps half the dose? I think there are some examples in the literature.

DR. SEEFF: Well, I know that you're looking into this issue of idiosyncratic liver disease and looking at suggestions that dose may be very important even there. The higher the dose, even for idiosyncratic reactors, the more likely they will get that liver injury. So seemingly that's a possibility.

And I suppose this is something that we might think about, but again I'm pretty convinced it’s so, at least in clinical situations. I'm not talking about the pharmaceutical testing being done in the early studies where you have to know, does this drug cause an injury? Therefore you may have a new drug that's a very important drug that could be pulled from the study and never reach the market. But I think in a clinical setting, when you rechallenge, you have to believe that there was no substitute for that particular medication, and that this was a serious liver toxic drug. So I'm very cautious, particularly when it comes to hepatocellular injury.

It may be that trying to do rechallenge with a lower

does may, in fact, give you information you need and if you have data to prove that, that will be fine.

DR. CHALASANI: But in case of statins when you have an elevated aminotransferase, you can treat them through the lower dose with the same statin. They seem to adapt to that.

DR. SEEFF: And then go back to the original dose or the same drug with a lower dose.

DR. CHALASANI: Actually, you can go back to the higher dose with rare exceptions. So I guess these are non-jaundiced cases.

DR. SEEFF: Yes.

DR. CHALASANI: These are just biochemical abnormalities.

DR. SEEFF: Right. I think once you have jaundice, it's a significant injury.

DR. KAPLOWITZ: Leonard, very nice talk. I just want to pursue the cholestatic injury. I'm not sure I entirely agree with you in terms of the safety of reintroducing the suspect drug or challenging people who've had a cholestatic reaction. Since we're recalling Hy Zimmerman, one of the things that he pointed out was that there're so-called bland cholestatic reactions, and let's say exudative ones where there's inflammation and maybe some element of liver injury. The bland ones I think we're beginning to see a number of examples where -- did I miss that?

DR. SEEFF: Well, what I said was that I think in general rechallenge is safe for the people with cholestatic liver disease, unless they have other manifestations such as fever, rash and some of the manifestations are simple immuno-allergic --

DR. KAPLOWITZ: Yes.

DR. SEEFF: -- liver-related disease. Under those circumstances, I think one has to be just as cautious.

DR. KAPLOWITZ: Right. So in the bland circumstances, I guess a good example is, you know, are BSEP inhibitors like cyclosporine, where probably just a dose adjustment is all that's really needed. In the more exudative type of reactions we see examples of patients going on to develop irreversible progressive liver disease --

DR. SEEFF: Yes.

DR. KAPLOWITZ: -- and ductopenia and ultimately in a small percentage, cirrhosis and the need for a liver transplant. I find it sobering that the European registries are identifying, mortality associated with cholestatic reactions, whether or not patients manifest allergic features clinically.

DR. SEEFF: The syndrome may also evolve under these circumstances. So I think that challenging is always dangerous, and one has to be awfully cautious. I'm just saying that in general, in comparison, I think that the acute hepatocellular injury is much more likely to run into trouble as you

rechallenge than cholestatic liver disease. But the point's well taken that even cholestatic liver disease is an issue, and certainly Andrade has been showing it. Some of his patients who did poorly indeed had cholestatic liver disease. Yes, sir.

DR. WALLIS: Wallis from Seattle. I'm wondering if there's experience with actual desensitization? For example, in allopurinol hepatotoxicity, do we know if the drug can be administered again at very low doses where people are ultimately desensitized.

DR. SEEFF: I guess that's the point that Naga was making to some extent.

DR. WALLIS: Yes, but in that setting, it's with the eosinophils and rash and so forth, where we were just discussing the notion that it may in fact be more hazardous to rechallenge. Do you have any further thoughts on that?

DR. SEEFF: Well, to have thoughts, I need to have data and I frankly don't know the data, but perhaps Paul Watkins could tell me about the possibility of desensitizing patients. Particularly I think there would be a concern if there are so-called allergic manifestations. That bothers me terribly but it may be the case. I suspect that there are people here in the audience that have much more data than I have at my fingertips who may want to comment about that, but I don't know about it. You look as though you have something to say, Dr. Bonkovsky.

DR. BONKOVSKY: No.

DR. SENIOR: Leonard, you chided me for assigning you a hard topic on which there was no literature. We thank you for this very thoughtful discussion and raising many of the essential questions. Now what about the clinical value -- you said that the, the positive rechallenge was pretty strong evidence --

UNIDENTIFIED SPEAKER: Can’t hear you. We lost you.

DR. SENIOR: What about a negative rechallenge? Is there very strong evidence that we do not appreciate as to its value, even if well done?

DR. SELIGMAN: The question is about negative rechallenge.

UNIDENTIFIED SPEAKER: Please repeat the question.

DR. SEEFF: Yes. The question was if there's a positive rechallenge, then there seems to be real evidence that this was a drug-induced liver injury because this is what you were trying to do, to prove that that was the case. What happens if, in fact, you give the drug again and there is no signal and the patient doesn't develop signs? As I mentioned, I think that that does not necessarily preclude the possibility the likelihood that the drug was, in fact, implicated. Now there are mechanisms presumably that may account for this, and this may, in fact, be explainable but I don't think that a negative challenge absolutely precludes a diagnosis of drug-induced liver injury at all.